(12) UK Patent Application (19) GB (11) 2 407 318 (13) A

(43) Date of A Publication 27.04.2005

(21) Application No: 0324761.6

(22) Date of Filing: 23.10.2003

(51) INT CL[7]:
C07D 471/04 , A61P 1/00 11/06 17/06 17/10 19/02 29/00 37/08 , // C07D 209/12 401/06 409/06 417/06 (C07D 401/06 209:12 213:51 215:14 333:58) (C07D 409/06 209:12 333:28) (C07D 417/06 209:12 277:28 277:64) (C07D 471/04 209:12 211:84 233:24)

(52) UK CL (Edition X):
C2C CAA
U1S S1318 S1321 S2416

(56) Documents Cited:
EP 1170594 A2
EP 0620214 A1
WO 2003/066046 A1
WO 1991/006537 A2
US 3629284 A

(58) Field of Search:
Other: "ONLINE: CAS-ONLINE"

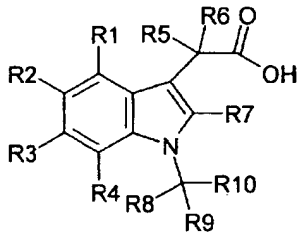
(71) Applicant(s):
Oxagen Limited
(Incorporated in the United Kingdom)
91 Milton Park, ABINGDON, Oxon,
OX14 4RY, United Kingdom

(72) Inventor(s):
David Middlemass
Mark Richard Ashton
Edward Andrew Boyd
Frederick Arthur Brookfield

(74) Agent and/or Address for Service:
Alison C Roberts
7 Comfrey Close, WOKINGHAM, Berkshire,
RG40 5YN, United Kingdom

(54) Abstract Title: **Substituted Indol-3-yl acetic acid derivatives**

(57) Compounds of general formula (I):

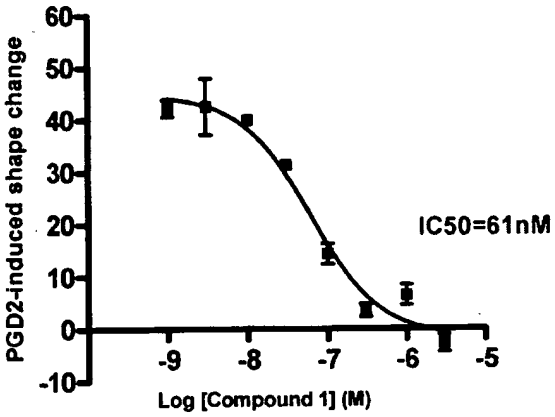


I

wherein
R^1, R^2, R^3 and R^4 are hydrogen, halo, C_1-C_6 alkyl, -O(C_1-C_6 alkyl), -CON(R^{11})$_2$, -SOR^{11}, -SO_2R^{11}, -SO_2N(R^{11})$_2$, -N(R^{11})$_2$, -NR^{11}COR^{11}, -CO_2R^{11}, -COR^{11}, -SR^{11}, -OH, -NO_2 or -CN;
each R^{11} is hydrogen or C_1-C_6 alkyl;
R^5 and R^6 are each hydrogen, or C_1-C_6 alkyl or together form a C_3-C_7 cycloalkyl group;
R^7 is hydrogen or C_1-C_6 alkyl;
R^8 is an optionally substituted aromatic moiety other than benzothiazole,
R^9 and R^{10} are each hydrogen, or C_1-C_6 alkyl or together form a C_3-C_7 cycloalkyl group;
and their pharmaceutically acceptable salts, hydrates, solvates, complexes or prodrugs are useful in the preparation of pharmaceuticals for the treatment of allergic diseases such as asthma, allergic rhinitis and atopic dermatitis.

GB 2 407 318 A

FIGURE 1


60
50
40
30
20
10
0
-10
PGD2-induced shape change
IC50=61nM
-9
-8
-7
-6
-5
Log [Compound 1] (M)

USE OF COMPOUNDS IN THERAPY

The present invention relates to the use of certain compounds in the treatment and prevention of allergic diseases such as asthma, allergic rhinitis and atopic dermatitis and other inflammatory diseases mediated by prostaglandin D_2 (PGD_2) acting at the CRTH2 receptor on cells including eosinophils, basophils and Th2 lymphocytes.

PGD_2 is an eicosanoid, a class of chemical mediator synthesised by cells in response to local tissue damage, normal stimuli or hormonal stimuli or *via* cellular activation pathways. Eicosanoids bind to specific cell surface receptors on a wide variety of tissues throughout the body and mediate various effects in these tissues. PGD_2 is known to be produced by mast cells, macrophages and Th2 lymphocytes and has been detected in high concentrations in the airways of asthmatic patients challenged with antigen (Murray *et al*, (1986), *N. Engl. J. Med.* **315**: 800-804). Instillation of PGD_2 into airways can provoke many features of the asthmatic response including bronchoconstriction (Hardy *et al*, (1984) *N. Engl. J. Med.* **311**: 209-213; Sampson *et al*, (1997) *Thorax* **52**: 513-518) and eosinophil accumulation (Emery *et al*, (1989) *J. Appl. Physiol.* **67**: 959-962).

The potential of exogenously applied PGD_2 to induce inflammatory responses has been confirmed by the use of transgenic mice overexpressing human PGD_2 synthase which exhibit exaggerated eosinophilic lung inflammation and Th2 cytokine production in response to antigen (Fujitani *et al*, (2002) *J. Immunol.* **168**: 443-449).

The first receptor specific for PGD_2 to be discovered was the DP receptor which is linked to elevation of the intracellular levels of cAMP. However, PGD_2 is thought to mediate much of its proinflammatory activity through interaction with a G protein-coupled receptor termed CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells) which is expressed by Th2 lymphocytes, eosinophils and basophils (Hirai *et al*, (2001) *J. Exp. Med.* **193**: 255-261, and EP0851030 and EP-A-1211513 and Bauer *et al*, EP-A-1170594). It seems clear that the effect of PGD_2 on

the activation of Th2 lymphocytes and eosinophils is mediated through CRTH2 since the selective CRTH2 agonists 13,14 dihydro-15-keto-PGD_2 (DK-PGD_2) and 15R-methyl-PGD_2 can elicit this response and the effects of PGD_2 are blocked by an anti-CRTH2 antibody (Hirai *et al*, 2001; Monneret *et al*, (2003) *J. Pharmacol. Exp. Ther.* **304**: 349-355). In contrast, the selective DP agonist BW245C does not promote migration of Th2 lymphocytes or eosinophils (Hirai *et al*, 2001; Gervais *et al*, (2001) *J. Allergy Clin. Immunol.* **108**: 982-988). Based on this evidence, antagonising PGD_2 at the CRTH2 receptor is an attractive approach to treat the inflammatory component of Th2–dependent allergic diseases such as asthma, allergic rhinitis and atopic dermatitis.

EP-A-1170594 suggests that the method to which it relates can be used to identify compounds which are of use in the treatment of allergic asthma, atopic dermatitis, allergic rhinitis, autoimmune disease, reperfusion injury and a number of inflammatory conditions, all of which are mediated by the action of PGD_2 at the CRTH2 receptor.

Compounds which bind to CRTH2 are taught in WO-A-03066046 and WO-A-03066047. These compounds are not new but were first disclosed, along with similar compounds, in GB 1356834, GB 1407658 and GB 1460348, where they were said to have anti-inflammatory, analgesic and antipyretic activity. WO-A-03066046 and WO-A-03066047 teach that the compounds to which they relate are modulators of CRTH2 receptor activity and are therefore of use in the treatment or prevention of obstructive airway diseases such as asthma, chronic obstructive pulmonary disease (COPD) and a number of other diseases including various conditions of bones and joints, skin and eyes, GI tract, central and peripheral nervous system and other tissues as well as allograft rejection.

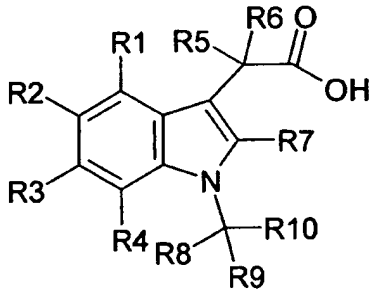
PL 65781 and JP 43-24418 also relate to indole derivatives which are similar in structure to indomethacin and, like indomethacin, are said to have anti-inflammatory and antipyretic activity. Thus, although this may not have been appreciated at the

time when these documents were published, the compounds they describe are COX inhibitors, an activity which is quite different from that of the compounds of the present invention. Indeed, COX inhibitors are contraindicated in the treatment of many of the diseases and conditions, for example inflammatory bowel disease for which the compounds of the present invention are useful, although they may sometimes be used to treat arthritic conditions.

Indole derivatives are also disclosed in WO-A-9950268. These compounds have a carboxylic acid moiety attached to the indole nitrogen atom. There is no suggestion that these compounds could be useful in the treatment of conditions such as asthma and allergic conditions, which are mediated by PGD_2. Rather, they are said to be of use in the treatment of complications arising from diabetes mellitus.

We have now discovered that compounds similar to a compound exemplified in EP-A-1170594 are antagonists of PGD_2 at the CRTH2 receptor and are useful in a method for the treatment of diseases and conditions mediated by PGD_2 at the CRTH2 receptor, the method comprising administering to a patient in need of such treatment a suitable amount of one of the compounds.

Therefore, in a first aspect of the invention, there is provided the use of a compound of general formula (I):



I

wherein

R^1, R^2, R^3 and R^4 are independently hydrogen, halo, C_1-C_6 alkyl, -O(C_1-C_6 alkyl),

$-CON(R^{11})_2$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, $-N(R^{11})_2$, $-NR^{11}COR^{11}$, $-CO_2R^{11}$, $-COR^{11}$, $-SR^{11}$, -OH, $-NO_2$ or -CN;

each R^{11} is independently hydrogen or $-C_1$-C_6 alkyl;

R^5 and R^6 are each independently hydrogen, or C_1-C_6 alkyl or together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group;

R^7 is hydrogen or C_1-C_6 alkyl;

R^8 is an aromatic moiety other than benzothiazole, optionally substituted with one or more substituents selected from halo, phenyl, C_1-C_6 alkyl, $-O(C_1$-$C_6)$alkyl, $-CON(R^{11})_2$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, $-N(R^{11})_2$, $-NR^{11}COR^{11}$, $-CO_2R^{11}$, $-COR^{11}$, $-SR^{11}$, -OH, $-NO_2$ or -CN;

wherein R^{11} is as defined above;

R^9 and R^{10} are each independently hydrogen, or C_1-C_6 alkyl or together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group;

or a pharmaceutically acceptable salt, hydrate, solvate, complex or prodrug thereof;

in the preparation of an agent for the treatment or prevention of diseases and conditions mediated by PGD_2 at the CRTH2 receptor.

Such diseases and conditions include allergic asthma, perennial allergic rhinitis, seasonal allergic rhinitis, atopic dermatitits, contact hypersensitivity (including contact dermatitis), food allergies, eosinophilic gastroenteritis, inflammatory bowel disease, ulcerative colitis and Crohn's disease, mastocytosis and also other PGD_2-mediated diseases, for example autoimmune diseases such as hyper IgE syndrome and systemic lupus erythematus, psoriasis, acne, multiple sclerosis, allograft rejection, reperfusion injury, chronic obstructive pulmonary disease, as well as, in some cases, rheumatoid arthritis, psoriatic arthritis and osteoarthritis.

Although some compounds to which the invention relates are known, there is no suggestion in most cases that they can be used for the treatment of diseases and conditions mediated by the action of PGD_2 at the CRTH2 receptor. EP-A-1170594 relates to methods of identifying compounds which are active at the CRTH2 receptor. It teaches that a compound which is similar to general forumula (I) except

that the substituent at the R^8 position is benzothiazole is a CRTH2 antagonist. However, there is no suggestion that such use would extend to compounds having other types of aryl substituent in this position.

In the present specification "C_1-C_6 alkyl" refers to a straight or branched saturated hydrocarbon chain having one to six carbon atoms and optionally substituted with one or more halo substituents or with one or more C_3-C_7 cycloalkyl groups. Examples include methyl, ethyl, n-propyl, isopropyl, t-butyl, n-hexyl, trifluoromethyl, 2-chloroethyl, methylenecyclopropyl, methylenecyclobutyl, methylenecyclobutyl and methylenecyclopentyl.

"C_1-C_4 alkyl" and "C_1-C_{18} alkyl" have similar meanings except that they contain from one to four and from one to eighteen carbon atoms respectively.

C_3-C_7 cycloalkyl refers to a saturated 3 to 7 membered carbocyclic ring. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In the present specification, "halo" refers to fluoro, chloro, bromo or iodo.

The terms "aromatic moiety" and "aryl" in the context of the present specification refer to an aromatic ring system having from 5 to 14 ring carbon atoms and containing up to three rings, one or more of which may be replaced by a nitrogen, oxygen or sulphur atom. Examples of aromatic moieties are benzene, pyridine, naphthalene, biphenyl, quinoline, isoquinoline, quinazoline, thiazole, benzoxazole, benzimidazole, thiophene, benzthiophene, imidazo[1,2-a]pyridine, indole, indazole and imidazole ring systems.

Appropriate pharmaceutically and veterinarily acceptable salts of the compounds of general formulae (I) and (II) include basic addition salts such as sodium, potassium, calcium, aluminium, zinc, magnesium and other metal salts as well as choline, diethanolamine, ethanolamine, ethyl diamine and other well known basic addition

salts.

Where appropriate, pharmaceutically or veterinarily acceptable salts may also include salts of organic acids, especially carboxylic acids, including but not limited to acetate, trifluoroacetate, lactate, gluconate, citrate, tartrate, maleate, malate, pantothenate, adipate, alginate, aspartate, benzoate, butyrate, digluconate, cyclopentanate, glucoheptanate, glycerophosphate, oxalate, heptanoate, hexanoate, fumarate, nicotinate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, proprionate, tartrate, lactobionate, pivolate, camphorate, undecanoate and succinate, organic sulphonic acids such as methanesulphonate, ethanesulphonate, 2-hydroxyethane sulphonate, camphorsulphonate, 2-naphthalenesulphonate, benzenesulphonate, p-chlorobenzenesulphonate and p-toluenesulphonate; and inorganic acids such as hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, hemisulphate, thiocyanate, persulphate, phosphoric and sulphonic acids.

Salts which are not pharmaceutically or veterinarily acceptable may still be valuable as intermediates.

Prodrugs are any covalently bonded compounds which release the active parent drug according to general formula (I) *in vivo*. Examples of prodrugs include alkyl esters of the compounds of general formula (I), for example the esters of general formula (II) below.

If a chiral centre or another form of isomeric centre is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereoisomers, are intended to be covered herein. Compounds of the invention containing a chiral centre may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone.

In the compounds of general formula (I), it is preferred that, independently or in any

combination:

R^1 is halo or hydrogen;

R^2 is halo or hydrogen;

R^3 is halo or hydrogen;

R^4 is halo or hydrogen.

In more preferred compounds, R^1, R^3 and R^4 are hydrogen, while R^2 is halo, particularly fluoro.

In preferred compounds of general formula (I), R^5 and R^6 are each independently hydrogen or C_1-C_4 alkyl. However, in more active compounds, at least one, and preferably both of R^5 and R^6 are hydrogen.

Similarly, it is preferred that R^9 and R^{10} are each independently hydrogen or C_1-C_4 alkyl and in more active compounds, at least one of R^9 and R^{10} is hydrogen.

Compounds of general formula (I) preferably have an R^7 group chosen from H, C_1-C_6 alkyl; most suitably R^7 is methyl.

Among the most preferred compounds are the following:

1. (5-Fluoro-2-methyl-1-quinolin-2-ylmethyl-*1H*-indol-3-yl)-acetic acid;
2. [1-(5-Chloro-benzo[b]thiophen-3-ylmethyl)-5-fluoro-2-methyl-*1H*-indol-3-yl]-acetic acid;
3. (5-Fluoro-2-methyl-1-naphthalen-2-ylmethyl-*1H*-indol-3-yl)-acetic acid;
4. [1-(5-Chloro-thiophen-2-ylmethyl)-5-fluoro-2-methyl-*1H*-indol-3-yl]-acetic acid;
5. [1-(4-Chloro-benzyl)-5-fluoro-2-methyl-*1H*-indol-3-yl]-acetic acid;
6. (5-Fluoro-2-methyl-1-naphthalen-1-ylmethyl-*1H*-indol-3-yl)-acetic acid;
7. [5-Fluoro-2-methyl-1-(8-methyl-1,8a-dihydro-imidazo[1,2-a]pyridin-2-ylmethyl)-*1H*-indol-3-yl]-acetic acid;
8. (5-Fluoro-2-methyl-1-pyridin-2-ylmethyl-*1H*-indol-3-yl)-acetic acid;

9. (5-Fluoro-2-methyl-1-pyridin-3-ylmethyl-*1H*-indol-3-yl)-acetic acid;
10. (5-Fluoro-1-isoquinolin-1-ylmethyl-2-methyl-*1H*-indol-3-yl)-acetic acid;
11. [5-Fluoro-2-methyl-1-(2-methyl-thiazol-4-ylmethyl)-*1H*-indol-3-yl]-acetic acid;
12. [5-Fluoro-2-methyl-1-(2-phenyl-thiazol-4-ylmethyl)-*1H*-indol-3-yl]-acetic acid;
13. [5-Fluoro-1-(4-fluoro-benzoyl)-2-methyl-*1H*-indol-3-yl]-acetic acid;
14. [6-Fluoro-1-(6-fluoro-quinolin-2-ylmethyl)-2-methyl-1H-indol-3-yl]-acetic acid;

or the C_1-C_6 alkyl esters of any of the above.

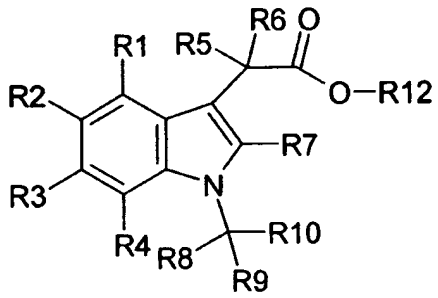
Compounds 1 to 14 are new and themselves form a further aspect of the invention together with their C_1-C_6 alkyl, aryl, $(CH_2)_mOC(=O)C_1$-C_6alkyl, $(CH_2)_mN(R^{13})_2$ or $CH((CH_2)_mO(C=O)R^{14})_2$ esters; wherein

m is 1 or 2;

R^{13} is hydrogen or methyl;

R^{14} is C_1-C_{18} alkyl.

The compound of general formula (I) may be derived *in vivo* from a prodrug. The prodrug may be a compound of general formula (II):



II

wherein R^1, R^2, R^3, R^4, R^5 , R^6, R^7, R^8, R^9 and R^{10} are as defined for general formula (I); R^{12} is C_1-C_6 alkyl, aryl, $(CH_2)_mOC(=O)C_1$-C_6alkyl, $(CH_2)_mN(R^{13})_2$, $CH((CH_2)_mO(C=O)R^{14})_2$;

m is 1 or 2;

R^{13} is hydrogen or methyl;

R^{14} is C_1-C_{18} alkyl.

Therefore, in a further aspect of the invention there is provided the use of a compound of general formula (II) as defined above in the preparation of an agent for the treatment or prevention of diseases and conditions mediated by PGD_2 at the CRTH2 receptor.

Examples of particularly suitable R^{12} groups when the compound of general formula (II) is used as a prodrug include:

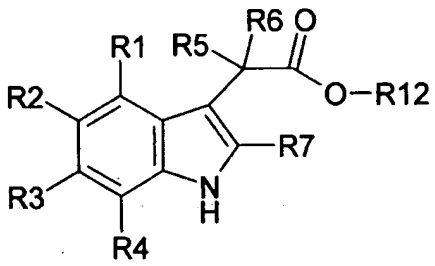
methyl, ethyl, propyl, phenyl, $-CH_2OC(=O)tBu$, $-CH_2CH_2N(Me)_2$, $-CH_2CH_2NH_2$ or $-CH(CH_2O(C=O)R^{14})_2$ wherein R^{14} is as defined above.

When the compound of general formula (II) acts as a prodrug, it is later transformed to the drug by the action of an esterase in the blood or in a tissue of the patient.

Preferred compounds of general formula (II) include the esters of Compounds 1 to 15 above. These compounds are new and themselves form a further aspect of the invention

Compounds of general formula (I) may be prepared from compounds of general formula (II) in which R^{12} is C_1-C_6 alkyl by hydrolysis with an alkali such as sodium or lithium hydroxide. The reaction may take place in an aqueous solvent or an organic solvent or a mixture of the two. A typical solvent used for the reaction is a mixture of tetrahydrofuran and water

Compounds of general formula (II) may be prepared from compounds of general formula (III):



III

wherein R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined for general formula (I) and R^{12} is C_1-C_6 alkyl;

by reaction with a compound of general formula (IV):

$$R^8\text{-}C(R^9R^{10})\text{-}X \qquad \text{(IV)}$$

wherein R^8, R^9 and R^{10} are as defined for general formula (I) and X is a leaving group, particularly a halo group such as chloro or bromo;

in the presence of a strong base, for example sodium hydride.

Compounds of general formulae (III) and (IV) are well known and are readily available or can be prepared by methods well known to those skilled in the art.

Compounds of general formula (I) are antagonists of PGD_2 at the CRTH2 receptor and compounds of general formula (II) are prodrugs for compounds of general formula (I). Compounds of general formulae (I) and (II) are therefore useful in a method for the treatment of diseases and conditions mediated by PGD_2 at the CRTH2 receptor, the method comprising administering to a patient in need of such treatment a suitable amount of a compound of general formula (I) or (II).

In a further aspect of the invention, there is provided a novel compound of general formula (I) or (II) for use in medicine, particularly for use in the treatment or prevention of diseases and conditions mediated by PGD_2 at the CRTH2 receptor.

As mentioned above, such diseases and conditions include allergic asthma, perennial allergic rhinitis, seasonal allergic rhinitis, atopic dermatitits, contact hypersensitivity (including contact dermatitis), food allergies, eosinophilic gastroenteritis, inflammatory bowel disease, ulcerative colitis and Crohn's disease, mastocytosis and also other PGD_2-mediated diseases, for example autoimmune diseases such as hyper IgE syndrome and systemic lupus erythematus, psoriasis, acne, multiple sclerosis, allograft rejection, reperfusion injury, chronic obstructive pulmonary disease, as well as rheumatoid arthritis, psoriatic arthritis and osteoarthritis.

The compounds of general formula (I) or (II) must be formulated in an appropriate manner depending upon the diseases or conditions they are required to treat.

Therefore, in a further aspect of the invention there is provided a pharmaceutical composition comprising a novel compound of general formula (I) or (II) together with a pharmaceutical excipient or carrier. Other active materials may also be present, as may be considered appropriate or advisable for the disease or condition being treated or prevented.

The carrier, or, if more than one be present, each of the carriers, must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient.

The formulations include those suitable for oral, rectal, nasal, bronchial (inhaled), topical (including eye drops, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration and may be prepared by any methods well known in the art of pharmacy.

The route of administration will depend upon the condition to be treated but preferred compositions are formulated for oral, nasal, bronchial or topical administration.

The composition may be prepared by bringing into association the above defined active agent with the carrier. In general, the formulations are prepared by uniformly and intimately bringing into association the active agent with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product. The invention extends to methods for preparing a pharmaceutical composition comprising bringing a novel compound of general formula (I) or (II) in conjunction or association with a pharmaceutically or veterinarily acceptable carrier or vehicle.

Formulations for oral administration in the present invention may be presented as: discrete units such as capsules, sachets or tablets each containing a predetermined amount of the active agent; as a powder or granules; as a solution or a suspension of the active agent in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water in oil liquid emulsion; or as a bolus etc.

For compositions for oral administration (e.g. tablets and capsules), the term "acceptable carrier" includes vehicles such as common excipients e.g. binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone (Povidone), methylcellulose, ethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sucrose and starch; fillers and carriers, for example corn starch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid; and lubricants such as magnesium stearate, sodium stearate and other metallic stearates, glycerol stearate stearic acid, silicone fluid, talc waxes, oils and colloidal silica. Flavouring agents such as peppermint, oil of wintergreen, cherry flavouring and the like can also be used. It may be desirable to add a colouring agent to make the dosage form readily identifiable. Tablets may also be coated by methods well known in the art.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active agent in a free flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative,

surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active agent.

Other formulations suitable for oral administration include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active agent in an inert base such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active agent in a suitable liquid carrier.

For topical application to the skin, compounds of general formula (I) or (II) may be made up into a cream, ointment, jelly, solution or suspension etc. Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics such as the British Pharmacopoeia.

Compounds of general formula (I) or (II) may be used for the treatment of the respiratory tract by nasal, bronchial or buccal administration of, for example, aerosols or sprays which can disperse the pharmacological active ingredient in the form of a powder or in the form of drops of a solution or suspension. Pharmaceutical compositions with powder-dispersing properties usually contain, in addition to the active ingredient, a liquid propellant with a boiling point below room temperature and, if desired, adjuncts, such as liquid or solid non-ionic or anionic surfactants and/or diluents. Pharmaceutical compositions in which the pharmacological active ingredient is in solution contain, in addition to this, a suitable propellant, and furthermore, if necessary, an additional solvent and/or a stabiliser. Instead of the propellant, compressed air can also be used, it being possible for this to be produced as required by means of a suitable compression and expansion device.

Parenteral formulations will generally be sterile.

Typically, the dose of the compound will be about 0.01 to 100 mg/kg; so as to maintain the concentration of drug in the plasma at a concentration effective to inhibit PGD_2 at the CRTH2 receptor. The precise amount of a compound of general formula (I) or (II) which is therapeutically effective, and the route by which such compound is best administered, is readily determined by one of ordinary skill in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

Compounds of general formula (I) or (II) may be used in combination with other active agents which are useful for the treatment of allergic and other inflammatory diseases mediated by PGD_2 at the CRTH2 receptor.

Therefore, the pharmaceutical composition described above may contain one or more additional active agents useful in the treatment of diseases and conditions mediated by PGD_2 at the CRTH2 receptor.

These additional active agents are not necessarily inhibitors of PGD_2 at the CRTH2 receptor – they may have a completely different mode of action.

There is also provided the use of a compound of general formula (I) or (II) in the preparation of an agent for the treatment of diseases and conditions mediated by PGD_2 at the CRTH2 receptor, wherein the agent also comprises an additional active agent.

Examples of such additional active agents include existing therapies for allergic and other inflammatory diseases including:
β2 agonists such as salmeterol;
corticosteroids such as fluticasone;
antihistamines such as loratidine;
leukotriene antagonists such as montelukast;
anti-IgE antibody therapies such as omalizumab;

anti-infectives such as fusidic acid (particularly for the treatment of atopic dermatitis);

anti-fungals such as clotrimazole (particularly for the treatment of atopic dermatitis);

immunosuppressants such as tacrolimus and particularly pimecrolimus in the case of inflammatory skin disease.

CRTH2 antagonists may also be combined with therapies that are in development for inflammatory indications including:

other antagonists of PGD_2 acting at other receptors such as DP antagonists;

inhibitors of phoshodiesterase type 4 such as cilonilast;

drugs that modulate cytokine production such as inhibitors of TNFα converting enzyme (TACE);

drugs that modulate the activity of Th2 cytokines IL-4 and IL-5 such as blocking monoclonal antibodies and soluble receptors;

PPAR-γ agonists such as rosiglitazone;

5-lipoxygenase inhibitors such as zileuton.

In yet a further aspect of the invention, there is provided a product comprising a novel compound of general formula (I) or (II) and one or more of the agents listed above as a combined preparation for simultaneous, separate or sequential use in the treatment of a disease or condition mediated by the action of PGD_2 at the CRTH2 receptor.

The invention will now be described in greater detail with reference to the following non limiting examples and the drawing in which:

Figure 1 shows the effect of Compound 1 on PGD_2 mediated eosinophil shape change.

Example 1 – Preparation of Compounds of general formula (I)

1. **Synthesis of (5-Fluoro-2-methyl-1-quinolin-2-ylmethyl-*1H*-indol-3-yl)-acetic acid ethyl ester**

(5-Fluoro-2-methyl-*1H*-indol-3-yl)-acetic acid ethyl ester (3.00 g, 12.75 mmol) in DMSO (10 ml) was added dropwise over 1 min to a stirred solution of sodium hydride (1.30 g, 32.50 mmol; 60 % in mineral oil) in DMSO (30 ml) under nitrogen at room temperature. The mixture was stirred at room temperature for 30 min and then 2-chloromethyl-quinoline hydrochloride (2.73 g, 12.75 mmol) was added. The resulting mixture was stirred at room temperature for 16 h, then water (50 ml) was added and the product was extracted into ethyl acetate (3 x 100 ml). The combined organic extracts were dried and concentrated *in vacuo* to leave a residue which was purified by flash chromatography on silica gel (Flashmaster™, 70 g scale column) eluting with 0 % ethyl acetate : hexane to 20 % ethyl acetate : hexane over one hour to give the *quinoline* (1.50 g, 31 %) as a pale brown solid, Tr = 1.53 min, m/z (ES^+) $(M+H)^+$ 377.54.

2. **Synthesis of Compound 1 – (5-Fluoro-2-methyl-1-quinolin-2-ylmethyl-*1H*-indol-3-yl)-acetic acid**

Lithium hydroxide monohydrate (0.67 g, 15.95 mmol) was added in one portion to a stirred solution of (5-fluoro-2-methyl-1-quinolin-2-ylmethyl-*1H*-indol-3-yl)-acetic acid ethyl ester (1.50 g, 3.98 mmol) in tetrahydrofuran : water (20 ml; 1:1). The mixture was stirred at room temperature for 2 h and then the mixture adjusted to pH 6 with concentrated hydrochloric acid. The product was extracted into ethyl acetate (3 x 15 ml) and the combined organic extracts were dried and concentrated *in vacuo* to give the *carboxylic acid* (0.81 g, 58 %) as a pale brown solid, δ_H (400 MHz, DMSO) 8.27 (1H, d *J* 8.4 Hz, *Ar*), 7.98 (1H, d *J* 8.6 Hz ,*Ar*), 7.93 (1H, d *J* 7.2 Hz, *Ar*), 7.77 (1H, dt *J* 6.9 1.5 Hz, *Ar),* 7.59 (1H, dt *J* 6.9 1.1 Hz, *Ar*), 7.45 (1H, dd *J* 8.9 4.4 Hz, *Ar*), 7.24 (1H, dd *J* *9.9* 2.5, *Ar*), 6.90-6.85 (2H, m, *Ar*), 5.68 (2H, s, NCH_2),

3.64 (2H, s, CH_2COOH), 2.37 (3H, s. CH_3), Tr = 1.3, m/z (ES^+) $(M+H)^+$ 349.17.

Compounds 2 to 15 were prepared using the same general method as Compound 1 but using appropriately chosen starting materials.

Compound 2 – [1-(5-Chloro-benzo[b]thiophen-3-ylmethyl)-5-fluoro-2-methyl-*1H*-indol-3-yl]-acetic acid

Tr = 2.11 min (100 %), m/z (ES^+) $(M+H)^+$ 388.06.

Compound 3 – (5-Fluoro-2-methyl-1-naphthalen-2-ylmethyl-*1H*-indol-3-yl)-acetic acid

Tr = 1.59 min (96 %), m/z (ES^+) $(M+H)^+$ 348.01.

Compound 4 – [1-(5-Chloro-thiophen-2-ylmethyl)-5-fluoro-2-methyl-*1H*-indol-3-yl]-acetic acid

Tr = 1.58 min (97 %), m/z (ES^+) $(M+H)^+$ 338.01.

Compound 5 – [1-(4-Chloro-benzyl)-5-fluoro-2-methyl-*1H*-indol-3-yl]-acetic acid

Tr =1.60 min (93%), m/z $(ES)^+$ $(M+H)^+$ 332.01.

Compound 6 – (5-Fluoro-2-methyl-1-naphthalen-1-ylmethyl-*1H*-indol-3-yl)-acetic acid

Tr =1.60 min (90%), m/z $(ES)^+$ $(M+H)^+$ 348.01.

Compound 7 – [5-Fluoro-2-methyl-1-(8-methyl-1,8a-dihydro-imidazo[1,2-a]pyridin-2-ylmethyl)-*1H*-indol-3-yl]-acetic acid

Tr =1.03 min (100 %), m/z (ES^+) $(M+H)^+$ 352.19.

Compound 8 – (5-Fluoro-2-methyl-1-pyridin-2-ylmethyl-*1H*-indol-3-yl)-acetic acid

Tr = 0.97 min, (100 %), m/z (ES^+) $(M+H)^+$ 299.17.

Compound 9 – (5-Fluoro-2-methyl-1-pyridin-3-ylmethyl-*1H*-indol-3-yl)-acetic acid

Tr = 0.95 min (83 %), m/z (ES^+) $(M+H)^+$ 299.18.

Compound 10 – (5-Fluoro-1-isoquinolin-1-ylmethyl-2-methyl-*1H*-indol-3-yl)-acetic acid

Tr =1.18 min (89 %), (ES^+) $(M+H)^+$ 349.17.

Compound 11 – [5-Fluoro-2-methyl-1-(2-methyl-thiazol-4-ylmethyl)-*1H*-indol-3-yl]-acetic acid

Tr =1.35 min (92 %), m/z (ES^+) $(M+H)^+$ 319.14.

Compound 12 – [5-Fluoro-2-methyl-1-(2-phenyl-thiazol-4-ylmethyl)-*1H*-indol-3-yl]-acetic acid

Tr =1.66 min (98 %), m/z (ES^+) $(M+H)^+$ 381.15.

Compound 13 – [5-Fluoro-1-(4-fluoro-benzoyl)-2-methyl-*1H*-indol-3-yl]-acetic acid

Tr =1.47 min (88 %), m/z (ES^+) $(M+H)^+$ 330.30.

Compound 14 – [6-Fluoro-1-(6-fluoro-quinolin-2-ylmethyl)-2-methyl-1H-indol-3-yl]-acetic acid

δ_H (400 MHz, $CDCl_3$) 7.92-7.88 (1H, m, *Ar*), 7.57 (1H, d *J* 8.6 Hz, *Ar*), 7.30-7.25 (1H, m, *Ar*), 7.04 (2H, app td *J* 9.2, 2.7 Hz, *Ar*), 6.74-6.72 (1H, m, *Ar*), 6.53-6.46 (2H, m, *Ar*), 5.11 (2H, s, CH_2Ar), 3.38 (2H, s, CH_2CO_2H), 1.99 (3H, s, CCH_3); Tr =1.80 min (96 %), m/z (ES^+) $(M+H)^+$ 367.07.

Example 2 – Measurement of CRTH2 Antagonist Activity

Materials and Methods

Materials

Calcium-3 dye was purchased from Molecular Devices (Wokingham, UK). Mono-poly resolving medium was obtained from Dainippon Pharmaceuticals (Osaka, Japan). Macs anti-CD16 microbeads were from Miltenyi biotec (Bisley, Surrey). ChemoTx plates were purchased from Neuroprobe (Gaithesburg, MD). Poly-D-lysine coated 96-well plates were obtained from Greiner (Gloucestershire, UK). [^{3}H]PGD_2 was from Amersham Biosciences (Buckinghamshire, UK). [^{3}H]SQ29548 was purchased from Perkin Elmer Life Sciences (Buckinghamshire, UK). All other reagents were obtained from Sigma-Aldrich (Dorset, UK), unless otherwise stated.

Methods

Cell culture

Chinese Hamster Ovary cells were transfected with CRTH2 or DP receptors (CHO/CRTH2 and CHO/DP) and were maintained in culture in a humidified atmosphere at 37°C (5% CO_2) in Minimum Essential Medium (MEM) supplemented with 10% foetal bovine serum, 2 mM glutamine, and 1 mg ml^{-1} active G418. The cells were passaged every 2-3 days. For radioligand binding assay, cells were prepared in triple-layer flasks or in 175 cm^2 square flasks (for membrane preparation). For calcium mobilisation assay, cells were grown in a 96 well plate 24h prior to the assay at a density of 80,000 cells per well.

Isolation of eosinophils from fresh blood

Blood (100ml) was sampled from healthy donors into EDTA-treated tubes and used immediately in cell isolation. Peripheral blood leukocyte preparations of granulocytes (eosinophils and neutrophils) and mononuclear cells (monocytes and lymphocytes) were prepared by density gradient centrifugation on a metrizoate-based supporting medium, Mono-poly Resolving medium. Eosinophils were purified from

total granulocyte preparations by negative magnetic selection using anti-CD16 beads. Briefly, granulocytes were coated with anti-CD16 coated microbeads in PBS/2mM EDTA which selectively bind to neutrophils. Eosinophils were separated from neutrophils by passage of the cell suspension through a magnetic field and collection of the negative fraction.

Preparation of cell membranes

Membranes were prepared either from CHO/CRTH2 and CHO/DP cells, or from platelets (as a source of TP receptors). CHO cells grown to confluency were washed with PBS and detached using a Versene solution (15 ml per flask). When the cells were grown in 175 cm^2 square flask, they were collected by scrapping in PBS. The cell suspensions were centrifuged (1,700 rpm, 10 min, 4°C) and resuspended in 15 ml of buffer (1xHBSS, supplemented with 10 mM HEPES, pH 7.3). Cell suspensions were then homogenised using an Ultra Turrax at setting 4-6 for 20 s. The homogenate was centrifuged at 1,700 rpm for 10 min and the supernatant was collected and centrifuged at 20,000 rpm for 1h at 4°C. The resulting pellet was resuspended in buffer and stored at -80°C in aliquots of 200-500 µl. The protein concentration was determined by the method of Bradford (1976), using bovine serum albumin as standard. The platelets were washed by centrifugation at 600xg for 10 min and resuspended in ice-cold assay buffer (10 mM Tris-HCl, pH 7.4, 5 mM Glucose, 120 mM NaCl, 10 µM indomethacin) and directly centrifuged at 20,000 rpm for 30 min at 4°C. The resulting pellet was treated as described above.

Radioligand binding assays

$[^3H]PGD_2$ (160 Ci/mmol) binding experiments were performed on membranes prepared as described above. Assays were performed in a final volume of 100 µl of buffer (1XHBSS/HEPES 10 mM, pH 7.3). Cell membranes (15µg). Cell membranes 15mg were preincubated at room temperature with varying concentration of competing ligand for 15 min. $[^3H]PGD_2$ (mol, final concentration) was then added and the incubation continued for a further one hour at room temperature. The reaction was terminated by the addition of 200 µl ice-cold assay buffer to each well,

followed by rapid filtration through Whatman GF/B glass fibre filters using a Unifilter Cell harvester (PerkinElmer Life Sciences) and six washes of 300 µl of ice-cold buffer. The Unifilter plates were dried at room temperature for at least 1h and the radioactivity retained on the filters was determined on a Beta Trilux counter (PerkinElmer Life Sciences), following addition of 40 µl of Optiphase Hi-Safe 3 (Wallac) liquid scintillation. Non specific binding was defined in the presence of 10 µM unlabelled PGD_2. Assays were performed in duplicate.

The results of the radioligand binding experiments to the CRTH2 and DP receptors are shown in Tables 1 and 2.

Table 1 – Radioligand binding data (Ki on CRTH2 Receptor).

Compounds	Ki (nM)
Compound 1	38±16
Compound 14	5.3±2
Compound 6	9±1
Compound 3	9±1
Compound 2	82±31

Table 2 – Radioligand binding data (Ki on DP Receptor).

Compounds	Ki (nM)
Compound 1	8873±758
Compound 3	10990±2835
Compound 14	3785±2510

The TP receptor radioligand binding was done on membranes prepared from platelets. 15-40 µg of protein were pre-incubated with varying concentrations of competing ligand for 15 min at room temperature in assay buffer (10 mM Tris-HCl, pH 7.4, 5 mM glucose, 120 mM NaCl, 10 µM indomethacin). [^{3}H]SQ29548 (38 Ci/mmol, 10 nM final concentration) was then added and the incubation continued for a further 30 min at room temperature. The reaction was terminated by the addition of 200 µl ice-cold assay buffer to each well, followed by rapid filtration through Whatman GF/C glass fibre filters using a Unifilter Cell harvester

(PerkinElmer Life Sciences) followed with six washes of 300 µl of ice-cold buffer. The radioactivity was determined as described above.

All of the compounds studied in this assay bound to the TP receptor with low affinity (Ki>1µM).

Compounds of general formula (I) bound to CRTH2 receptor expressed in CHO cells with a range of affinity varying from very high to moderate. In fact the Ki values determined in competition versus [^{3}H]PGD_2 varied from 500 pM to 1 µM. Compounds of general formula (I) had no activity (or very weak activity) at the DP and TP receptors. The binding selectivity of the compounds of general formula (I) for CRTH2 receptor was greater than 200 fold for CRTH2 receptor, compared to DP and TP receptors.

Calcium mobilisation Assay

Cells were seeded onto poly-D-lysine coated 96-well plates at a density of 80,000 cells per well and incubated at 37°C overnight to allow the cells to adhere. Cells were washed twice with HBSS and incubated for 1h at 37°C in 100µl HBSS and 100µl calcium-3-dye (Molecular Devices), supplemented with 4mM probenecid. Changes in fluorescence were monitored over a 50s time course with agonist addition at 17s using a Flexstation (Molecular Devices).

Effect of CRTH2 agonists on calcium mobilisation in CHO-CRTH2 cells

PGD_2 caused a dose-dependent increase in intracellular Ca^{2+} mobilisation in CHO/CRTH2 cells, with an EC_{50} = 2.4 ± 0.5nM (n=3).

Effect of compounds of general formula (I) on the calcium mobilisation induced by PGD_2

PGD_2-stimulated Ca^{2+} flux was fully inhibited by the compounds of general formula (I) and the IC_{50} value for each compound in the calcium assay was comparable to its Ki value in Radioligand binding. IC_{50} values of compounds of general formula (I) varied from 5 nM to 1 µM. The results for several compounds of general formula (I) are shown in Table 3. Increasing doses of the compounds of general formula (I)

caused a dose-dependent and parallel shift of the PGD_2 dose response curve in CHO/CRTH2 cells, thereby indicating that the compounds are competitive CRTH2 antagonists.

The antagonistic effect of the compounds of general formula (I) appears to be CRTH2 selective, since no inhibitory effect was seen with ATP-stimulated Ca^{2+} flux.

Table 3 – Inhibition of PGD_2-induced calcium flux

Compounds	IC_{50} (nM)
Compound 1	91±15
Compound 14	48±16
Compound 6	933
Compound 7	158±21

Chemotaxis Assay

Eosinophils were purified by negative magnetic selection as described above. 25µl of cells at $3x10^6$cells/ml and test samples (29µl) prepared in RPMI 1640/10% FCS were applied to the upper and lower chambers of a 3µm-pore sized 96-well ChemoTx plate (Neuroprobe), respectively. After incubation at 37°C for 90 min, any cells remaining on top of the filter were wiped off and plates were centrifuged at 300xg, 2 min to collect any cells on the under-side of the filters. The upper membrane was carefully removed and cell migration was quantified by counting the number of migrated cells under a light microscope in 2 separate fields of vision. Background cell migration was determined by measuring the response to buffer alone.

PGD_2 induced a dose-dependent increase in eosinophil migration with an EC50 of 30 nM. This effect was also seen with the selective CRTH2 agonist indomethacin. The IC_{50} values of compounds of general formula (I) were comparable to their Ki values in ligand binding and their IC_{50} values in the calcium flux assay. The antagonistic effect of the compounds of general formula (I) appears to be CRTH2 selective, since

no inhibitory effect was seen when other chemoattractant compounds were used, including eotaxin, 5-oxo-ETE, IL-5, C5a, and LTB4.

The chemotaxis assay is the disease relevant assay for the compounds of general formula (I) but similar results can be obtained using the eosinophil shape change assay as described below.

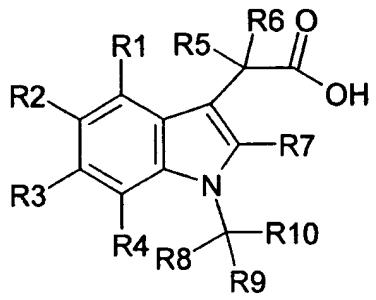
Eosinophil shape change Assay

Purified eosinophils were added to a 96-well plate at a density of 40,000 cells per well in RPMI supplemented with 10% FCS. Cells were stimulated with agonists for 1h, 37°C and any changes in cell morphology were measured by changes in their ability to scatter light when illuminated in a FACSCalibur flow cytometer (Becton Dickinson). Results were analysed using CellQuest software.

PGD_2 caused a dose dependent increase in the shape change of human eosinophils, as assessed by a shift of cells to region UR, reflecting increased forward scatter. This effect was fully and dose-dependently inhibited by compounds of general formula (I), as exemplified on Figure 1.

CLAIMS

1. The use of a compound of general formula (I):



I

wherein

R^1, R^2, R^3 and R^4 are independently hydrogen, halo, C_1-C_6 alkyl, -O(C_1-C_6 alkyl), $CON(R^{11})_2$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, $-N(R^{11})_2$, $-NR^{11}COR^{11}$, $-CO_2R^{11}$, $-COR^{11}$, $-SR^{11}$, -OH, $-NO_2$ or -CN;

each R^{11} is independently hydrogen or C_1-C_6 alkyl;

R^5 and R^6 are each independently hydrogen, or C_1-C_6 alkyl or together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group;

R^7 is hydrogen or C_1-C_6 alkyl;

R^8 is an aromatic moiety other than benzothiazole, optionally substituted with one or more substituents selected from halo, phenyl, C_1-C_6 alkyl, -O(C_1-C_6)alkyl, $-CON(R^{11})_2$,

$-SOR^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, $-N(R^{11})_2$, $-NR^{11}COR^{11}$, $-CO_2R^{11}$, $-COR^{11}$, $-SR^{11}$, -OH, $-NO_2$ or -CN;

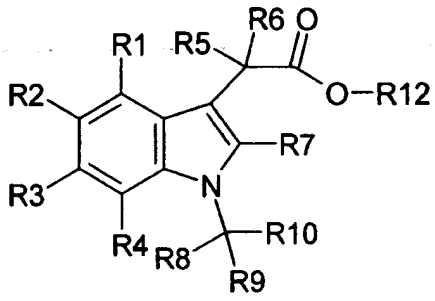
wherein R^{11} is as defined above;

R^9 and R^{10} are each independently hydrogen, or C_1-C_6 alkyl or together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group;

or a pharmaceutically acceptable salt, hydrate, solvate, complex or prodrug thereof;

in the preparation of an agent for the treatment or prevention of diseases and conditions mediated by PGD_2 at the CRTH2 receptor.

2. The use of a compound of general formula (II):



II

wherein R^1, R^2, R^3, R^4, R^5 , R^6, R^7, R^8, R^9 and R^{10} are as defined for general formula (I); R^{12} is C_1-C_6 alkyl, aryl, -$(CH_2)_mOC(=O)C_1$-C_6alkyl, -$(CH_2)_mN(R^{13})_2$, -$CH((CH_2)_mO(C=O)R^{14})_2$;

m is 1 or 2;

R^{13} is hydrogen or methyl;

R^{14} is C_1-C_{18} alkyl;

in the preparation of an agent for the treatment or prevention of diseases and conditions mediated by PGD_2 at the CRTH2 receptor.

3. The use as claimed in claim 1 or claim 2 wherein the disease or condition is allergic asthma, perennial allergic rhinitis, seasonal allergic rhinitis, atopic dermatitits, contact hypersensitivity (including contact dermatitis), food allergies, eosinophilic gastroenteritis, inflammatory bowel disease, ulcerative colitis and Crohn's disease, mastocytosis and also other PGD_2-mediated diseases, for example autoimmune diseases such as hyper IgE syndrome and systemic lupus erythematus, psoriasis, acne, multiple sclerosis, allograft rejection, reperfusion injury, chronic obstructive pulmonary disease, rheumatoid arthritis, psoriatic arthritis or osteoarthritis.

4. The use as claimed in any one of claims 1 to 3 wherein, in the compound of

general formula (I) or (II), independently or in any combination:

R^1 is halo or hydrogen;

R^2 is halo or hydrogen;

R^3 is halo or hydrogen;

R^4 is halo or hydrogen.

5. The use as claimed in claim 4 wherein, in the compound of general formula (I) or (II), R^1, R^3 and R^4 are hydrogen, while R^2 is halo.

6. The use as claimed in claim 5 wherein, in the compound of general formula (I) or (II), R^2 is fluoro.

7. The use as claimed in any one of claims 1 to 6, wherein, in the compound of general formula (I) or (II), R^5 and R^6 are each independently hydrogen or C_1-C_4 alkyl.

8. The use as claimed in claim 7, wherein in the compound of general formula (I) or (II), least one of R^5 and R^6 are hydrogen.

9. The use as claimed in any one of claims 1 to 8 wherein, in the compound of general formula (I) or (II), R^9 and R^{10} are each independently hydrogen or C_1-C_4 alkyl.

10. The use as claimed in claim 9 wherein, in the compound of general formula (I) or (II), at least one of R^9 and R^{10} is hydrogen.

11. The use as claimed in any one of claims 1 to 10 wherein, in the compound of general formula (I) or (II), R^7 is H or C_1-C_6 alkyl.

12. The use as claimed in claim 11 wherein, in the compound of general formula (I) or (II), R^7 is methyl.

13. The use as claimed in any one of claims 1 to 12 wherein the compound of general formula (I) or (II) is:

(5-Fluoro-2-methyl-1-quinolin-2-ylmethyl-*1H*-indol-3-yl)-acetic acid;

[1-(5-Chloro-benzo[b]thiophen-3-ylmethyl)-5-fluoro-2-methyl-*1H*-indol-3-yl]-acetic acid;

(5-Fluoro-2-methyl-1-naphthalen-2-ylmethyl-*1H*-indol-3-yl)-acetic acid;

[1-(5-Chloro-thiophen-2-ylmethyl)-5-fluoro-2-methyl-*1H*-indol-3-yl]-acetic acid;

[1-(4-Chloro-benzyl)-5-fluoro-2-methyl-*1H*-indol-3-yl]-acetic acid;

(5-Fluoro-2-methyl-1-naphthalen-1-ylmethyl-*1H*-indol-3-yl)-acetic acid;

(1-Benzothiazol-2-ylmethyl-5-fluoro-2-phenyl-*1H*-indol-3-yl)-acetic acid;

[5-Fluoro-2-methyl-1-(8-methyl-1,8a-dihydro-imidazo[1,2-a]pyridin-2-ylmethyl)-*1H*-indol-3-yl]-acetic acid;

(5-Fluoro-2-methyl-1-pyridin-2-ylmethyl-*1H*-indol-3-yl)-acetic acid;

(5-Fluoro-2-methyl-1-pyridin-3-ylmethyl-*1H*-indol-3-yl)-acetic acid;

(5-Fluoro-1-isoquinolin-1-ylmethyl-2-methyl-*1H*-indol-3-yl)-acetic acid;

[5-Fluoro-2-methyl-1-(2-methyl-thiazol-4-ylmethyl)-*1H*-indol-3-yl]-acetic acid;

[5-Fluoro-2-methyl-1-(2-phenyl-thiazol-4-ylmethyl)-*1H*-indol-3-yl]-acetic acid;

[5-Fluoro-1-(4-fluoro-benzoyl)-2-methyl-*1H*-indol-3-yl]-acetic acid;

[6-Fluoro-1-(6-fluoro-quinolin-2-ylmethyl)-2-methyl-1H-indol-3-yl]-acetic acid; or a C_1-C_6 alkyl, aryl, $(CH_2)_mOC(=O)C_1$-C_6alkyl, $(CH_2)_mN(R^{13})_2$ or $CH((CH_2)_mO(C=O)R^{14})_2$ ester of one of the above; wherein

m is 1 or 2;

R^{13} is hydrogen or methyl;

R^{14} is C_1-C_{18} alkyl.

14. (5-Fluoro-2-methyl-1-quinolin-2-ylmethyl-*1H*-indol-3-yl)-acetic acid;

[1-(5-Chloro-benzo[b]thiophen-3-ylmethyl)-5-fluoro-2-methyl-*1H*-indol-3-yl]-acetic acid;

(5-Fluoro-2-methyl-1-naphthalen-2-ylmethyl-*1H*-indol-3-yl)-acetic acid;

[1-(5-Chloro-thiophen-2-ylmethyl)-5-fluoro-2-methyl-*1H*-indol-3-yl]-acetic acid;

[1-(4-Chloro-benzyl)-5-fluoro-2-methyl-*1H*-indol-3-yl]-acetic acid;

(5-Fluoro-2-methyl-1-naphthalen-1-ylmethyl-*1H*-indol-3-yl)-acetic acid;

(1-Benzothiazol-2-ylmethyl-5-fluoro-2-phenyl-*1H*-indol-3-yl)-acetic acid;

[5-Fluoro-2-methyl-1-(8-methyl-1,8a-dihydro-imidazo[1,2-a]pyridin-2-ylmethyl)-*1H*-indol-3-yl]-acetic acid;

(5-Fluoro-2-methyl-1-pyridin-2-ylmethyl-*1H*-indol-3-yl)-acetic acid;

(5-Fluoro-2-methyl-1-pyridin-3-ylmethyl-*1H*-indol-3-yl)-acetic acid;

(5-Fluoro-1-isoquinolin-1-ylmethyl-2-methyl-*1H*-indol-3-yl)-acetic acid;

[5-Fluoro-2-methyl-1-(2-methyl-thiazol-4-ylmethyl)-*1H*-indol-3-yl]-acetic acid;

[5-Fluoro-2-methyl-1-(2-phenyl-thiazol-4-ylmethyl)-*1H*-indol-3-yl]-acetic acid;

[5-Fluoro-1-(4-fluoro-benzoyl)-2-methyl-*1H*-indol-3-yl]-acetic acid;

[6-Fluoro-1-(6-fluoro-quinolin-2-ylmethyl)-2-methyl-1H-indol-3-yl]-acetic acid; or a C_1-C_6 alkyl, aryl, $(CH_2)_mOC(=O)C_1$-C_6alkyl, $(CH_2)_mN(R^{13})_2$ or $CH((CH_2)_mO(C=O)R^{14})_2$ ester of one of the above; wherein

m is 1 or 2;

R^{13} is hydrogen or methyl;

R^{14} is C_1-C_{18} alkyl.

15. A compound as claimed in claim 14 for use in medicine, particularly for use in the treatment or prevention of diseases and conditions mediated by PGD_2 at the CRTH2 receptor.

16. A compound as claimed in claim 15 for use in the treatment or prevention of allergic asthma, perennial allergic rhinitis, seasonal allergic rhinitis, atopic dermatitits, contact hypersensitivity (including contact dermatitis), food allergies, eosinophilic gastroenteritis, inflammatory bowel disease, ulcerative colitis and Crohn's disease, mastocytosis and also other PGD_2-mediated diseases, for example autoimmune diseases such as hyper IgE syndrome and systemic lupus erythematus, psoriasis, acne, multiple sclerosis, allograft rejection, reperfusion injury, chronic obstructive pulmonary disease, as well as rheumatoid arthritis, psoriatic arthritis or osteoarthritis.

17. A pharmaceutical composition comprising a compound as claimed in claim 14 together with a pharmaceutical excipient or carrier.

18. A pharmaceutical composition as claimed in claim 17 formulated for oral, nasal, bronchial or topical administration.

19. A composition as claimed in claim 17 or claim 18, further containing one or more additional active agents useful in the treatment of diseases and conditions mediated by PGD_2 at the CRTH2 receptor.

20. A composition as claimed in claim 19, wherein the additional active agents are selected from:

β2 agonists such as salmeterol;

corticosteroids such as fluticasone;

antihistamines such as loratidine;

leukotriene antagonists such as montelukast;

anti-IgE antibody therapies such as omalizumab;

anti-infectives such as fusidic acid (particularly for the treatment of atopic dermatitis);

anti-fungals such as clotrimazole (particularly for the treatment of atopic dermatitis);

immunosuppressants such as tacrolimus and particularly pimecrolimus in the case of inflammatory skin disease;

other antagonists of PGD_2 acting at other receptors such as DP antagonists;

inhibitors of phoshodiesterase type 4 such as cilonilast;

drugs that modulate cytokine production such as inhibitors of TNFα converting enzyme (TACE);

drugs that modulate the activity of Th2 cytokines IL-4 and IL-5 such as blocking monoclonal antibodies and soluble receptors;

PPAR-γ agonists such as rosiglitazone;

5-lipoxygenase inhibitors such as zileuton.

21. A process for the preparation of a pharmaceutical composition as claimed in any one of claims 17 to 20 comprising bringing a compound as claimed in claim 14 in conjunction or association with a pharmaceutically or veterinarily acceptable carrier or vehicle.

22. A product comprising a compound as claimed in claim 14 and one or more of the agents listed in claim 20 as a combined preparation for simultaneous, separate or sequential use in the treatment of a disease or condition mediated by the action of PGD_2 at the CRTH2 receptor.

Application No: GB 0324761 6
Claims searched: 1-22

Examiner: Dave Cannon
Date of search: 27 February 2004

Patents Act 1977 : Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance	
X	1-3, 8-18 & 21	WO 91/06537 A2	(AMERICAN HOME PRODUCTS CORP) Pg 4 l.3-18, Generic formula outlined between pg 4 l 17, and pg 5 l 20 and specific examples 16, 17, 19, 20, 24-41
X	1-16	EP 0620214 A1	(ELI LILLY AND CO). Generic formulae I, III and especially V, and compounds outlined on pg 12-13, and several of examples between pg.20 and 46.
X	1-19 &21	WO 03/066046 A1	(ASTRAZENECA AB) Generic formula (I) on pg.1 and diseases outlined on pg.3 l 16 to pg.5 l.10.
X	13 & 14	US 3629284	(SUMITOMO CHEM CO.). Generic formula col 1, l 28-38 and compounds on col 3, l 1-12, and compound in col.9 l.49-50
X	13 & 14	EP 1170594 A2	(PFIZER PRODUCTS INC.) Compound (C), Fig. 10B, pg.34 and para. [0013] to [0025]

Categories

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art
Y	Document indicating lack of inventive step if combined with one or more other documents of same category	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC[W]

-

Worldwide search of patent documents classified in the following areas of the IPC[7]

-

The following online and other databases have been used in the preparation of this search report:

CAS-ONLINE